Study reveals how one form of natural vitamin E protects brain after stroke

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Blocking the function of an enzyme in the brain with a specific kind of vitamin E can prevent nerve cells from dying after a stroke, new research suggests.

In a study using mouse brain cells, scientists found that the tocotrienol form of vitamin E, an alternative to the popular drugstore supplement, stopped the enzyme from releasing fatty acids that eventually kill neurons.

The Ohio State University researchers have been studying how this form of vitamin E protects the brain in animal and cell models for a decade, and intend to pursue tests of its potential to both prevent and treat strokes in humans.

"Our research suggests that the different forms of natural vitamin E have distinct functions. The relatively poorly studied tocotrienol form of natural vitamin E targets specific pathways to protect against neural cell death and rescues the brain after stroke injury," said Chandan Sen, professor and vice chair for research in Ohio State's Department of Surgery and senior author of the study.

"Here, we identify a novel target for tocotrienol that explains how neural cells are protected."

The research appears online and is scheduled for later print publication in the *Journal of Neurochemistry*.

Vitamin E occurs naturally in eight different forms. The best-known form of vitamin E belongs to a variety called tocopherols. The form of vitamin E in this study, tocotrienol or TCT, is not abundant in the American diet but is available as a nutritional supplement. It is a common component of a typical Southeast Asian diet.

Sen's lab discovered tocotrienol vitamin E's ability to protect the brain 10 years ago. But this current study offers the most specific details about how that protection works, said Sen, who is also a deputy director of Ohio State's Heart and Lung Research Institute.

"We have studied an enzyme that is present all the time, but one that is activated after a stroke in a way that causes neurodegeneration. We found that it can be put in check by very low levels of tocotrienol," he said. "So what we have here is a naturally derived nutrient, rather than a drug, that provides this beneficial impact."

Sen and colleagues had linked TCT's effects to various substances that are activated in the brain after a stroke before they concluded that this enzyme could serve as an important therapeutic target. The enzyme is called cystolic calcium-dependent phospholipase A2, or cPLA2.

Following the trauma of blocked blood flow associated with a stroke, an excessive amount of glutamate is released in the brain. Glutamate is a neurotransmitter that, in tiny amounts, has important roles in learning and memory. Too much of it triggers a sequence of reactions that lead to the death of brain cells, or neurons - the most damaging effects of a stroke.

Sen and colleagues used cells from the hippocampus region of developing mouse brains for the study. They introduced excess glutamate to the cells to mimic the brain's environment after a stroke.

With that extra glutamate present, the cPLA2 enzyme releases a fatty acid called arachidonic acid into the brain. Under normal conditions, this fatty acid is housed within lipids that help maintain cell membrane stability.

But when it is free-roaming, arachidonic acid undergoes an enzymatic chemical reaction that makes it toxic - the final step before brain cells are poisoned in this environment and start to die. Activation of the cPLA2 enzyme is required to release the damaging fatty acid in response to insult caused by high levels of glutamate.

Sen and colleagues introduced the tocotrienol vitamin E to the cells that had already been exposed to excess glutamate. The presence of the vitamin decreased the release of fatty acids by 60 percent when compared to cells exposed to glutamate alone.

Brain cells exposed to excess glutamate followed by tocotrienol fared much better, too, compared to those exposed to only the damaging levels of glutamate. Cells treated with TCT were almost four times more likely to survive than were cells exposed to glutamate alone.

Though cPLA2 exists naturally in the body, blocking excessive function of this enzyme is not harmful, Sen explained. Scientists have already determined that mice genetically altered so they cannot activate the enzyme achieve their normal life expectancy and carry a lower risk for stroke.

Sen also noted that the amount of tocotrienol needed to achieve these effects is quite small - just 250 nanomolar, a concentration about 10 times lower than the average amount of tocotrienol circulating in humans who consume the vitamin regularly.

"So you don't have to gobble up a lot of the nutrient to see these effects,"

he said.

Provided by The Ohio State University